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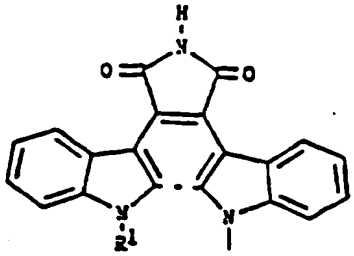
(54) Bezeichnung: AMINOSÄUREDERIVATE VON HETEROCYCLEN ALS PKC-INHIBITOREN



(III)

(57) Abstract

Described are aminoacid derivatives of the general formula (I), A-X-Y-E_w-R^5 in which A is a group of the general formula (III) in which R^1 is hydrogen or a lower-alkyl group with 1 to 4 carbon atoms and (- - -) is open or a bond. Also described is the use of such derivatives as inhibitors of protein kinase C in the treatment and/or prevention of cancer, viral infections, heart and circulatory disorders, thrombosis, cardiac-rythm irregularities, atherosclerosis, bronchopulmonary illnesses, degenerative conditions of the central nervous system, inflammatory illnesses, diseases of the immune system and psoriasis, and the use of such derivatives as immunosuppressants.

(57) Zusammenfassung

Aminosäurederivate der allgemeinen Formel (I): A-X-Y-E_w-R^5, in welcher A ein Rest der allgemeinen Formel (III), worin R^1 Wasserstoff oder ein niederer Alkylrest mit 1 bis 4 Kohlenstoffatomen ist und (- - -) offen oder eine Bindung sein kann und deren Verwendung als Inhibitoren der Protein-Kinase C der Behandlung und/oder Prävention von Krebs, Viruserkrankungen, Herz- und Gefäßerkrankungen, Thrombosen, Herzrhythmusstörungen, Atherosklerose, bronchopulmonalen Erkrankungen, degenerativen Erkrankungen des Zentralnervensystems, Entzündungskrankheiten, Krankheiten des Immunsystems, sowie Psoriasis oder zur Verwendung als Immunsupressivum.

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AMINO ACID DERIVATIVES OF HETEROCYCLES AS PROTEIN KINASE C INHIBITORS

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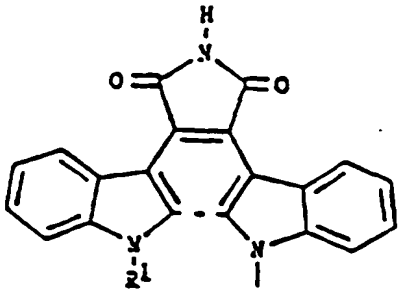


(III)

(57) Abstract

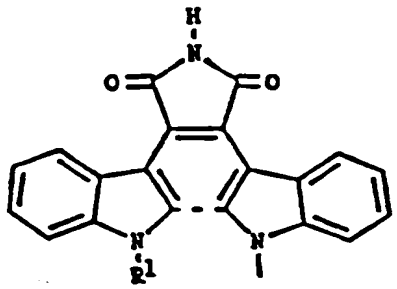
Described are aminoacid derivatives of the general formula (I), A-X-Y-E$_n$-R^5 in which A is a group of the general formula (III) in which R^1 is hydrogen or a lower-alkyl group with 1 to 4 carbon atoms and (- - -) is open or a bond. Also described is the use of such derivatives as inhibitors of protein kinase C in the treatment and/or prevention of cancer, viral infections, heart and circulatory disorders, thrombosis, cardiac-rythm irregularities, atherosclerosis, bronchopulmonary illnesses, degenerative conditions of the central nervous system, inflammatory illnesses, diseases of the immune system and psoriasis, and the use of such derivatives as immunosuppressants.

Description

The invention relates to new amino acid derivatives of the general formula I,

$$A\text{-}X\text{-}Y\text{-}E_n\text{-}R^5$$

in which A is a residue of the general formula III



where R^1 represents hydrogen or a lower alkyl residue with 1-4 carbon atoms and (- - -) can be open or can represent a bond;

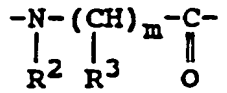
X represents a single bond or an alkylene group with 1-16 carbon atoms;

Y represents a single bond, a group such as $N\text{-}R^2$, CO, CS, CH=CH, PO(OH)O, SO_2, where

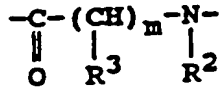
R^2 represents hydrogen or a lower alkyl residue with 1-4 carbon atoms, and

n = 1-20;

E represents either the same or different residues of the general formula IV



or of the general formula V



in which
R^2 represents a hydrogen or a lower alkyl residue with 1-4 hydrocarbons, and when

m = 1, the residue R^3 represents either hydrogen or the side group of one of the natural α-aminocarboxylic acids, and when m = 2-6, R^3 represents hydrogen; and

when E is a residue of formula IV, R^5 represents an amino group or a $-OR^4$ residue, in which R^4 represents a lower alkyl residue with 1-4 carbon atoms or hydrogen; and when E is a residue of formula V, it represents hydrogen.

Preferred compounds are those of the general formula I, in which A can represent bisindolylmaleinimide or indolopyrrolocarbazole of the general formula III, in which R^1 can be hydrogen or a lower alkyl residue with 1-4 carbon atoms, X is an alkylene group with 1-10 carbon atoms, Y is NH or CO, E is an aminocarboxylic acid of the general formula IV or the general formula V, in which R^2 is hydrogen, in which formula, when m = 1,

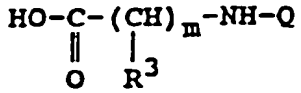
R^3 then is hydrogen or the side group of one of the natural α-aminocarboxylic acids, and when m = 1-6 [sic;2-6], R^3 is then hydrogen, and n is preferably 1-6. In the case of the terminal carboxylic acid present in the case of formula IV, it is also possible to have an amidation with ammonia or an esterification with a lower alcohol, such as methanol, ethanol or propanol.

Furthermore, preferred compounds of the general formula I are those in which A represents bisindolylmaleinimide or indolopyrrolocarbazole of the general formula III, in which R^1 represents methyl, X is methylene, propylene, butylene, pentylene, octylene and nonylene, and Y is either NH or CO, and $-E_n-R^5$ represents alanine, alanine methyl ester, β-alanine, arginine, serine, glycylalanine, glycylglycylalanine, glycylglycylglycylalanine, glycylglycylserine, lysylglycylalanine, serylglycylalanine, alanylglycyllysine, lysylasparaginylarginylphenylalanylalanine, β-alanylalanine, 4-aminovalerianoylserine or alanylarginine, as well as pharmacologically acceptable salts of acidic compounds of formula I with bases and [salts] of alkaline compounds of formula I with acids, methods for the preparation of compounds of formula I as well as drugs containing compounds of formula I.

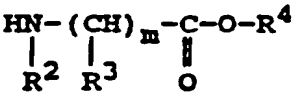
Compounds of the general formula I, in which A, X, Y and E have the above-indicated meanings and n = 1, are prepared either by reacting compounds of the general formula VI

A-X-Y-G

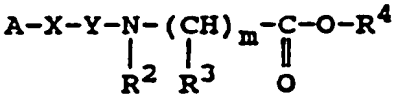
in which A and X have the above-indicated meanings and -Y-G is an amino group, with aminocarboxylic acids of the general formula VII,



in which R^3 has the meaning indicated above, and any functional groups present are provided with protecting groups, and Q is an amino protecting group such as tert-butoxycarbonyl, benzyloxycarbonyl or fluorenylmethyloxycarbonyl, followed by the cleavage of the protecting group using generally known methods (for the purpose of the reaction it is appropriate to convert the carboxylic acid group of compounds of the general formula VII using dicyclohexylcarbodiimide, pentafluorophenol or hydroxysuccinimide to activated carboxylic acid esters), or, by reacting compounds of the general formula VI, in which A and X have the above-indicated meanings, and Y represents CO, CS, CH=CH, PO(OH)O or SO_2, G is a hydroxy group or a halogen atom, with aminocarboxylic acids of the general formula VIII,

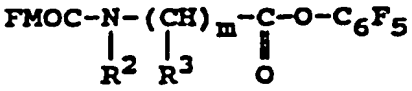


in which R^2 and R^3 have the meanings indicated above, and R^4 is a methyl, ethyl or propyl group, to form compounds of the general formula IX



in which R^2, R^3 and R^4 have the meanings indicated above. When the compounds of the general formula VI are carboxylic acids, the carboxylic acids are converted, for the purpose of the reaction, with compounds of the general formula VIII, under the usual conditions, to activated esters, such as pentafluorophenyl esters or hydroxysuccinimidyl esters. Compounds of the general formula IX are then converted by alkaline saponification of the ester group to compounds of the general formula I.

Compounds of the general formula I, in which A, X and Y have the meanings indicated above and E_n with $n > 1$ represents a peptide group, are prepared either by reacting compounds of the general formula I according to the generally known methods with additional aminocarboxylic acids or by synthesizing compounds of the general formula I on solid phases using the Merrifield method. For this purpose, the first amino acid of the general formula XI



in which R^2 and R^3 have the meanings indicated above is attached by condensation to the Merrifield resin, followed by the cleavage of the fluorophenylmethyloxycarbonyl protecting group according to generally known methods and, subsequently, depending on need, addition by condensation of additional aminocarboxylic acids of the general formula XI. In the last condensation step, the compounds of the general formula VI in which A and X have the meanings indicated above, Y represents CO or CS, and G is a hydroxy group, are reacted, in the presence of carboxylic acid activating compounds such as dicyclohexylcarbodiimide, with the peptide bound to the Merrifield resin. The cleavage of compounds of the general formula I from the resin occurs according to generally known methods, for example in trifluoroacetic acid in the presence of phenol. If the synthesis is conducted according to the usual methods, then the end products of the general formula I are present as carboxylic acid amides of the general formula Ia

$$A\text{-}X\text{-}Y\text{-}E_n\text{-}NH_2$$

if the syntheses are conducted on Wang resin, then the compounds of the general formula I are isolated as carboxylic acids.

Compounds of the general formula IV, in which A and X have the meanings indicated above, Y = NH_2 or Y = COOH, are known; their preparation has been described in the patent applications EP 0,328,026, EP 0,384,349, EP 0,397,060, and DE 4,217,964.5 and in Tetrahedron Lett. 1990, 31 (2353), Tetrahedron Lett. 1990, 31 (5201) and the literature cited therein.

The reaction of compounds of the general formula VI, in which A and X have the meanings indicated above, and Y represents $N-R^2$ and G is hydrogen, with aminocarboxylic acids of the general formula VII is conducted by placing an aminocarboxylic acid of the general formula VII into an aprotic solvent such as ethyl acetate, dichloromethane, DMSO, preferably DMF, and by converting it with pentafluorophenol or N-hydroxysuccinimide, preferably with dicyclohexylcarbodiimide, and in the presence of hydroxybenzotriazole, to an active carboxylic acid ester, followed by a reaction, in the same solvent, with compounds of the general formula VI at temperatures between 0-60°C, preferably at room temperature. The reaction products are purified using known methods, preferably a chromatographic method, and isolated.

The cleavage of the protecting group is also conducted according to generally standard methods; the cleavage of the preferably used tert-butyloxycarbonyl protecting group is conducted with strong acids such as hydrochloric acid; preferably it is conducted with trifluoroacetic acid in dichloromethane as solvent at temperatures between 0-35°C, preferably at room temperature. After neutralization of the reaction solution, products are isolated in pure form by precipitation in appropriate solvents.

Furthermore, compounds of the general formula I, in which A and X have the meanings indicated above and E has a terminal carboxylic acid group, can be manufactured by converting compounds of the general formula VI, in which A and X have the meanings indicated above, Y represents either CO or CS and G represents a hydroxy group, in an appropriate solvent, preferably

DMF, with pentafluorophenol or N-hydroxysuccinimide, preferably with dicyclohexylcarbodiimide and in the presence of hydroxybenzotriazole, to active carboxylic acid esters, followed by reacting it in the same solvent with compounds of the general formula VIII at temperatures between 0-60°C, preferably at room temperature. The isolation of the products of the general formula IX can be conducted successfully using standard methods, however it is preferably conducted by chromatography. The saponification of the carboxylic acid esters of the general formula IX to the desired compounds of the general formula I can be implemented in either an acidic or basic manner, preferably in the presence of alkali hydroxides in aqueous organic solvent mixtures, but preferably with lithium hydroxide in water/dioxane at temperatures between 0-40°C, preferably at room temperature. The products of the general formula I are isolated after chromatography and/or crystallization. Compounds of the general formula I, in which A and X have the meanings indicated above, Y represents a carbonyl group and E_n with n > 1 a peptide group, are prepared by attaching by condensation aminocarboxylic acids of the general formula XI, in which R^2 and R^3 have the meanings indicated above, in aprotic solvents such as DMF, preferably DMA, in the presence of hydroxybenzotriazole to Merrifield resins; excess reagents are washed with the solvent used, the fluorenylmethyloxycarbonyl protecting group is cleaved under alkaline conditions, preferably with piperidine at room temperature, residual reagents are again removed by washing, and in this manner additional amino acids are added by condensation and as a last partial [sic] compound, a compound of the general

formula VI, in which A and X have the meanings indicated above, Y represents CO, and G represents a hydrogen group, is added by condensation. These compounds are isolated by treating the Merrifield resin with a strong acid, preferably in the presence of trifluoroacetic acid and phenol, possibly thiophenol and thioanisole, for several hours, preferably more than 20, at room temperature; the dark red solution obtained is then separated and the products are isolated, after removal of the solvents, in solid form from ether. The products are obtained in pure form by chromatography on RP phase and/or by crystallization.

Compounds of general formula I, which have a chiral center, can be used as stereoisomer mixtures or in the form of enantiomers.

Basic compounds of the general formula I are converted, for the purpose of purification and for galenic reasons, preferably to crystalline, pharmacologically acceptable salts. The salts are prepared in the usual manner by neutralization of the bases with corresponding inorganic or organic acids. Possible acids are, for example, hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid, acetic acid, tartaric acid, lactic acid, citric acid, maleic acid, salicylic acid, ascorbic acid, malonic acid, fumaric acid, oxalic acid and succinic acid. The acid addition salts are prepared in a known manner by mixing the free base and their solutions with the corresponding acids or their solutions in an organic solvent, for example, a lower alcohol such as methanol, ethanol or 2-propanol or a lower ketone such as acetone or 2-butanone or an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran or dioxane.

Compounds of the general formula I are potent inhibitors of protein kinase C. Protein kinase C plays an important key role in intracellular signal transduction and it is closely connected with the regulation of contractile, secretory and proliferative processes. Because of these properties the compounds according to the invention can be used for the treatment and/or prevention of cancer, viral diseases (for example, HIV infection), cardiac and vascular diseases such as blood pressure, thrombosis, cardiac rhythm disorders, atherosclerosis, bronchopulmonary diseases, degenerative diseases of the central nervous system such as Alzheimer's disease, inflammatory diseases such as rheumatism and arthritis, diseases of the immune system such as allergies, and psoriasis. In addition, the substances can be used as immunosuppressants.

From the literature, synthetic derivatives and compounds which are derived from substructures of the staurosporin aglycone are known as potent inhibitors of protein kinase C (J. Med. Chem. 1992, 35, 177, J. Med. Chem. 1992, 35, 994). Their mechanism of action is based on expulsion of ATP from the catalytic subunit of the protein kinase C.

With the compounds according to the invention of the general formula I, a new group of PKC inhibitors has been found. They contain additionally an amino acid portion, which is derived on the one hand from a substrate of PKC, with high affinity, represented by the amino acid serine, and on the other hand from an inhibitor, represented by the amino acid alanine (Science 1987, 238, 1726, Cell. Signalling 1990, 2, 187). Surprisingly, these new compounds of the general formula I not only have been shown to be highly potent, but also, as shown in some examples,

selective inhibitors of protein kinase C. Their effect on the MLC kinase was shown to be considerably weaker.

The compounds can be administered in the formulation appropriate for the individual cases, either enterally or parenterally, in doses from 1-500 mg/kg, preferably 1-50 mg/kg.

The compounds according to the invention of the general formula I can be administered orally or parenterally in liquid or solid form. The injection solution used primarily is water, which contains the usual additives for injection solutions such as stabilization means, solution enhancers or buffers. Such additives are, for example, tartrate and citrate buffers, ethanol, complexing agents (such as ethylenediaminetetraacetic acid) and their nontoxic salts as well as high molecular weight polymers (such as liquid polyethylene oxide) for regulation of the viscosity. Solid support substances are, for example, starches, lactose, mannitol, methylcellulose, talcum, highly dispersed silicic acids, high molecular weight fatty acids (such as stearic acid), gelatin, agar, calcium phosphate, magnesium stearate, fats of animal or plant origin, solid high molecular weight polymers (such as polyethylene glycol); preparations which are suitable for oral administration may contain, if desired, additional flavoring and/or sweetening substances.

The following comparative tests illustrate the inhibitory effect of the compounds according to the invention of the general formula I on protein kinase C.

The enzyme protein kinase C (PKC) is obtained in pure form after extraction from rat brains. Its activity is determined with labeled 32-phosphorus in a synthetic peptide, which is derived from the PKC "pseudosubstrate" sequence (amino acids 19-

31 of the PKC sequence with alanine substituted in position 25 for serine). The reaction mixture with a volume of 200 µL contains the following components: 50 mM Tris-HCl, pH 7.5, 5 mM $MgCl_2$, 1 mM DTT, 4 µM free Ca^{2+}, 10 µM ATP, 1 µg phosphatidylserine, 0.2 µg 1,2-diolein and 0.3 µg peptide substrate. The mixture is preincubated for 4 min at 30°C and the reaction is started then by the addition of 5 nM PKC. After 5 min of incubation at 30°C the reaction is stopped with 0.73% H_3PO_4 and the sample is then filtered through a nitrocellulose filter (0.1 µm pore size). The phosphate incorporation is determined by Cerenkov counting in the scintillation counter.

Table I shows the results from this test for a selection of examples. The selectivity of these compounds with regard to other kinases, such as myosin light chain kinase, was verified with a few examples. These values are represented in Table II.

Table I. Enzyme test PKC with peptide substrate [Ser^{25}]PKC(19-31)

Beispiel ①	Inhibition IC_{50}(nM) ②
1	14
1a	6.3
1b	23
2	28
2a	25
2b	220
2c	>100
2d	>1000
2e	>1000
2f	330
3	61
4	36
4a	18
5	580
7	230
7a	>100
7b	>100
7c	200
7d	>1000
7e	340
7f	570
8	38
9	190
10	9.6

Key: 1 Example
2 Inhibition IC_{50} (nM)

Table II. Enzyme test PKC with peptide substrate [Ser^{25}]PKC(19-31) and myosin light chain kinase

① Beispiel	Hemmung der Proteinkinasen ② IC_{50} (nM)		Verhältnis IC_{50} MLC-Kinase/ ③ IC_{50} C-Kinase
	PKC	MLC-Kinase	
1	14	4600	328
1a	6.3	1900	302
1b	23	2400	104
A	130	1300	10

Key: 1 Example
2 Inhibition of protein kinases
3 Ratio IC_{50} MLC kinase/IC_{50} C kinase

A: 3-(1-(3-aminopropyl)-3-indolyl)-4-(1-methyl-3-indolyl)-1H-pyrrol-2,5-dione (European Patent No. 0,328,026)

The following examples are used to illustrate the invention further:

Example 1

2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-L-serylaminopropyl)-1H-indol-3-yl)maleinimide

100 mg (0.2 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3(N-FMOC-seryl)aminopropyl)-1H-indol-3-yl)maleinimide are dissolved in 5 mL dichloromethane, reacted with 1 mL piperidine and stirred at room temperature for 1 h. The solvent is distilled in a vacuum, the residue dissolved in 10 mL diisopropyl ether and stirred vigorously. The residue is separated, stirred again into diethyl ether, and then 15 mg (21%) of the product are isolated in the form of a red solid substance with a melting point of 136-140°C. Rf = 0.11 (dichloromethane:menthanol [sic; methanol] = 90:10%).

The 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3(N-FMOC-L-seryl)aminopropyl)-1H-indol-3-yl)maleinimide used as a precursor is prepared as follows:

200 mg (0.2 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3(N-FMOC-O-tert-butyl-L-seryl)aminopropyl)-1H-indol-3-yl)maleinimide in 1 mL dichloromethane are reacted at room temperature with 5 mL of trifluoroacetic acid and stirred for 3 h. The dilution is conducted with 50 mL dichloromethane, followed by neutralization with saturated $NaHCO_3$ solution and drying of the organic phase over Na_2SO_4. After the removal by distillation of the solvent in a vacuum, the residue is precipitated in ether. 210 mg (100%) of the products with a melting point of 133-135°C are isolated. Rf = 0.39 (dichloromethane:methanol = 90:10%).

The 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3(N-FMOC-O-tert-butyl-L-seryl)aminopropyl)-1H-indol-3-yl)maleinimide used as starting material is prepared as follows:

100 mg (0.3 mmol) 2-[(1-methyl)-1H-indol-3-yl]-3-[1-(3-aminopropyl)-1H-indol-3-yl)maleinimide, dissolved in 5 mL acetic acid, are reacted with 138 mg (0.3 mmol) N-FMOC-O-tert-butyl-serinepentafluorophenyl ester and 20 mg of 1-hydroxy-1H-benzotriazole and stirred for 3 h at room temperature. It is diluted with 50 mL acetic acid, followed by washing of the organic phase with water, drying over Na_2SO_4 and removal of the solvent by vacuum distillation. The residue is dissolved in 10 mL acetic acid. In this process a part of the products (120 mg) is prepared in clean form. The mother liquor is separated by column chromatography (silica gel, cyclohexane:acetic acid = 50:50%). Another 60 mg of the products are isolated (yield: 180 mg, 94.2%). Rf = 0.71 (dichloromethane:methanol = 90:10%).

In a manner similar to the Example 1 and the indicated method, the following are prepared:

1a) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-L-alanylaminopropyl)-1H-indol-3-yl)maleinimide. Melting point: 95-103°C; Rf = 0.12 (dichloromethane:methanol = 90:10%);

1b) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-ß-alanylaminopropyl)-1H-indol-3-yl)maleinimide. Melting point: 118-127°C; Rf = 0.19 (chloroform:methanol:concentrated NH_3 = 250:50:8).

Example 2

2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-D-alanylaminopropyl)-1H-indol-3-yl)maleinimide

115 mg (0.2 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-N-BOC-D-alanylaminopropyl)-1H-indol-3-yl)maleinimide are dissolved in 5 mL dichloromethane, reacted with 3 mL trifluoroacetic acid and stirred for 6 h at room temperature. The reaction solution is diluted with 50 mL dichloromethane, neutralized with $NaHCO_3$ solution and dried over Na_2SO_4. After removal of the solvent by vacuum distillation the residue is separated on preparative thick-layer [sic] plates (silica gel, dichloromethane:methanol/saturated with NH_3 = 90:10%). After the extraction 56 mg (60%) of the product are isolated from diisopropyl ether, as a solid substance with a melting point of 108-118°C. Rf = 0.15 (dichloromethane:methanol/sat. NH_3 = 90:10%).

The 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-N-BOC-D-alanylaminopropyl)-1H-indol-3-yl)maleinimide used as precursor is prepared as follows:

80 mg (0.2 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-aminopropyl)-1H-indol-3-yl)maleinimide are dissolved in 2 mL acetic acid and 1 mL DMF and reacted with 58 g (0.2 mmol) N-BOC-D-alanine-O-succinimidyl ester. The mixture is stirred for 18 hours at room temperature, diluted with 50 mL acetic acid and the organic phase is washed twice with water. The organic phase is dried over Na_2SO_4 and the solvent is removed from that phase by

vacuum distillation. The residue (115 mg) is used without additional purification for the next step.

In a manner similar to Example 2 and by the indicated method, the following are prepared:

2a) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(4-L-alanylaminobutyryl)-1H-indol-3-yl)maleinimide. Melting point 90-102°C; Rf = 0.15 (dichloromethane:methanol/sat. NH_3 = 90:10%);

2b) 2-((1-Methyl)-1H-indol-3-yl)-3-(1-(4-L-arginylaminobutyl)-1H-indol-3-yl)maleinimide. Melting point 158-172°C; Rf = 0.42 (chloroform:methanol:conc. NH_3 = 250:50:8);

2c) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(5-L-alanylaminopentyl)-1H-indol-3-yl)maleinimide. Melting point 96-106°C; Rf = 0.12 (dichloromethane:methanol = 90:10%);

2d) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(9-L-alanylaminononyl)-1H-indol-3-yl)maleinimide. Melting point 90-95°C; Rf = 0.12 (dichloromethane:methanol = 90:10%);

2e) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(9-L-serylaminononyl)-1H-indol-3-yl)maleinimide. Melting point 95-97°C; Rf = 0.24 (dichloromethane:methanol = 90:10%);

2f) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(9-L-alanylaminooctyl)-1H-indol-3-yl)maleinimide. Melting point 80-91°C; Rf = 0.16 (dichloromethane:methanol = 90:10%);

2g) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(9-L-serylaminooctyl)-1H-indol-3-yl)maleinimide. Melting point 86-94°C; Rf = 0.72 (chloroform:methanol:conc. NH_3 = 250:50:8).

Example 3

2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(5-L-serylaminopentanoyl)-aminopropyl)-1H-indol-3-yl)maleinimide

40 mg (0.05 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(5-(N-FMOC-L-seryl)aminopentanoyl)aminopropyl)-1H-indol-3-yl)-maleinimide are dissolved in 4 mL anhydrous THF, reacted with 40 mg (0.5 mmol) diethylamine and stirred for 18 h at room temperature. The solvent is then removed by vacuum distillation and the residue is separated by thick-layer chromatography (silica gel, dichloromethane:methanol/sat. NH_3 = 90:10%). The fraction with an Rf value of 0.52 is isolated, and the product is extracted. After removal of the solvent by vacuum distillation, 15 mg (51%) of the product with a melting point of 145-175°C are isolated.

The 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(5-(N-FMOC-L-seryl)aminopentanoyl)aminopropyl)-1H-indol-3-yl)maleinimide used as a precursor is prepared as follows:

13 mg (0.015 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(5-(N-FMOC-O-tert-butyl-L-seryl)aminopentanoyl)aminopropyl)-1H-indol-3-yl)maleinimide are dissolved in 1 mL dichloromethane and reacted in the presence of 4 mL trifluoroacetic acid over 2 days. After dilution with 50 mL dichloromethane, neutralization is conducted with aqueous $NaHCO_3$ solution, followed by drying of the organic phase over Na_2SO_4. After the removal of the solvent by vacuum distillation the residue is stirred in ether/n-pentane,

removed by suction [filtration] and dried. 10 mg (83%) of the product are isolated.

The 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(5-(N-FMOC-O-tert-butyl-L-seryl)aminopentanoyl)aminopropyl)-1H-indol-3-yl)maleinimide used as precursor is prepared in a manner similar to the one used in Example 1 from 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(4-aminopentanoyl)aminopropyl)-1H-indol-3-yl)maleinimide (yield: 29%).

The 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(4-aminopentanoyl)aminopropyl)-1H-indol-3-yl)maleinimide used as precursor was prepared from 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(4N-FMOC-aminopentanoyl)-aminopropyl)-1H-indol-3-yl)maleinimide by cleavage of the FMOC group in a manner similar to that used in Example 1 (yield 69%).

The 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(4N-FMOC-aminopentanoyl)-aminopropyl)-1H-indol-3-yl)maleinimide used as precursor was prepared by a reaction of 2-((1-methyl)-1-H-indol-3-yl)-3-(1-(3-aminopropyl)-1H-indol-3-yl)maleinimide with 5N-FMOC-aminovalerianic acid pentafluorophenyl ester in a manner similar to Example 1. Rf = 0.54 (dichloromethane:methanol/sat. NH_3 = 90:10%).

Example 4

2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(L-alanylglycyl)aminopropyl)-1H-indol-3-yl)maleinimide

95 mg (0.15 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(N-BOC-L-alanylseryl)aminopropyl)-1H-indol-3-yl)maleinimide were dissolved in 4 mL dichloromethane and stirred after the addition of 175 mg trifluoroacetic acid for 24 h at room temperature. After dilution with 50 mL dichloromethane, it is neutralized with aqueous $NaHCO_3$ solution, the organic phase is dried over Na_2SO_4, and the solvent is removed by vacuum distillation. The residue is separated by thick-layer chromatography (silica gel, dichloromethane:methanol/sat. NH_3 = 90:10%). The fraction with Rf = 0.37 is isolated, and the raw product is extracted from it; after removal of the solvent by vacuum distillation 16 mg (20%) of the desired product with a melting point of 126-138°C are obtained.

The 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(N-BOC-L-alanylseryl)-aminopropyl)-1H-indol-3-yl)maleinimide used as precursor is prepared as follows:

200 mg (0.5 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-aminopropyl)-1H-indol-3-yl)maleinimide, 185 mg (0.5 mmol) N-BOC-alanylglycine and 155 mg (0.75 mmol) dicyclohexylcarbodiimide are dissolved consecutively in a solvent mixture made of 3 mL anhydrous THF and 2 mL DMF, and reacted for 6 h at room temperature. The reaction mixture is poured into 300 mL water, the organic components are extracted with dichloromethane, the

organic phase is washed with water and dried over Na_2SO_4. After removal of the solvent by vacuum distillation the residue is separated by thick-layer chromatography (silica gel, dichloromethane:methanol= 90:10%). The fraction with an Rf value of 0.41 is separated, the product is extracted and isolated in the form of a red resin after removal of the solvent by vacuum distillation.

In a manner similar to Example 4 and the indicated method, the following is prepared:

4a) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(L-alanyl-ß-alanyl)aminopropyl)-1H-indol-3-yl)maleinimide. Melting point 103-112°C; Rf = 0.36 (chloroform:methanol:conc. NH_3 = 250:50:8))

Example 5

3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-alanine

100 mg (0.2 mmol) 3-(3(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-alanine methyl ester are dissolved in a mixture of 4 mL dioxane and 1 mL water, reacted with 36 mg (1.5 mmol) lithium hydroxide and stirred for 18 h at room temperature. The solvent is then removed by vacuum distillation, the residue is dissolved in 30 mL of acetic acid, washed with 1N HCl and dried over Na_2SO_4. The solvent is then removed by vacuum distillation and the residue is separated by thick-layer chromatography (silica gel, dichloromethane:methanol/sat. NH_3 = 90:10%). The product is

separated with the first polar fraction, extracted, and then the solvent is removed from it, and it is stirred into a mixture of dichloromethane:diisopropyl ether = 1:1. 65 mg (67%) of the product with a melting point of 240-255°C are isolated; Rf = 0.06 (chloroform:methanol:conc. NH_3 = 250:50:8).

Example 6

3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-alanine methyl ester

272 mg (0.65 mmol) 3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionic acid are dissolved in 3 mL anhydrous THF and reacted with 145 mg (0.70 mmol) dicyclohexylcarbodiimide and a mixture of 90 mg (0.8 mmol) alanine ethyl ester hydrochloride and 85 mg triethylamine, dissolved in 5 mL anhydrous THF. After stirring for 24 h at room temperature, followed by removal of the solvent by vacuum distillation, the residue is dissolved in 100 mL acetic acid and the organic phase is washed with water. After drying over Na_2SO_4 and removal by vacuum distillation of the solvent, the raw product is separated by thick-layer chromatography (silica gel, dichloromethane:methanol = 90:10%). The fraction with Rf = 0.31 is separated, the product is extracted and after removal of the solvent in a vacuum 130 mg (40%) of the product with a melting point of 142-149°C are isolated.

The 3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-

indol-1-yl)propionic acid used as precursor is prepared as follows:

210 mg (0.5 mmol) 3-(3-(4-(1-methylindol-3-yl)-furan-2,5-dion-3-yl)-indol-1-yl)propionic acid are dissolved in 2 mL DMF, reacted with 4 mL of a concentrated ammonium hydroxide solution and heated for 6 h at boiling point. After allowing the solution to cool, 200 mL of water are poured into it, and the product is extracted by extraction with acetic acid. The organic phase is washed twice with water, dried over Na_2SO_4 and the solvent is removed in a vacuum. The product is isolated at a yield of 82%. Melting point 244-253°C.

The 3-(3-(4-(1-methylindol-3-yl)-furan-2,5-dion-3-yl)-indol-1-yl)propionic acid used as precursor is prepared as follows:

0.5 g (1.2 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(2-cyanethyl)-1H-indol-3-yl)maleinimide is heated in an aqueous 10% solution of KOH for 3 h with reflux. The cooled reaction solution is acidified with acetic acid, the red precipitate is removed by suction [filtration], washed to neutrality and stirred in a mixture of methanol and water. After drying, 0.4 g (80%) of the product is isolated as an ocher-colored powder.

The following syntheses were conducted on solid phases with the RAMPS[R] synthesis apparatus; RAPIDAMIDE-Raisin manufactured by the Du Pont company was used as solid phase material.

Example 7

3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-alanylglycyl-L-lysinamide

0.1 mmol resin is activated according to the instructions and reacted over a period of 1 h with 0.4 mmol FMOC-L-arginine(Pmc)-OPfp in 2.5 mL acetic acid dimethylamide in the presence of 1-hydroxy-1H-benzotriazole. Excess reagents were washed out, the FMOC protecting group was removed with piperidine and the resin was again washed with acetic acid dimethylamide. Subsequently, glycine, L-alanine and 2-((1-methyl)-1H-indol-3-yl)-3-(1-(2-hydroxycarbonylethyl)-1H-indol-3-yl)maleinimide were added in the same manner by condensation. Subsequently, the product is cleaved by treatment of the resins over an 18 h period in a mixture of 300 mg phenol in 2 mL trifluoroacetic acid. The dark red reaction solution is removed by filtration, the solvent is removed in a vacuum, and the raw product is precipitated by treatment with ether. The solid precipitate is removed by suction [filtration], and then stirred in acetic acid, again removed by suction [filtration] and subjected to a washing step with ether. 15 mg of the product with a melting point of 158-160°C were isolated; Rf = 0.55 (butanol:pyridine:acetic acid:water = 30:20:6:24).

In a manner similar to Example 7 and the indicated method the following are prepared:

7a) 3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-lysyl-L-asparaginyl-L-arginyl-L-

phenylalanyl-L-alaninamide. Melting point 193-195°C; Rf = 0.48 (butanol:pyridine:acetic acid:water = 30:20:6:24).

7b) 3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionylglycylglycyl-L-alaninamide. Melting point 125-130°C; Rf = 0.74 (2-propanol:acetic acid:water = 4:1:1).

7c) 3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionylglycylglycyl-L-serylamide. Melting point 142-146°C; Rf = 0.71 (2-propanol:acetic acid:water = 4:1:1).

7d) 3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-serylglycyl-L-alaninamide. Melting point 165-167°C; Rf = 0.73 (2-propanol:acetic acid:water = 4:1:1).

7e) 3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionylglycylglycylglycyl-L-alanylamide. Melting point 157-159°C; Rf = 0.65 (2-propanol:acetic acid:water = 4:1:1).

7f) 3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-lysylglycyl-L-alanylamide. Melting point 146-148°C; Rf = 0.47 (2-propanol:acetic acid:water = 4:1:1).

Example 8

12-(2-(3-L-alanyl)aminopropyl(-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole

50 mg (0.1 mmol) 12-(2-(N-BOC-L-alanyl)aminopropyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole are dissolved in 5 mL dichloromethane at room temperature and reacted with 3 mL of trifluoroacetic acid. After stirring at this temperature for 3 h, dilution with

50 mL of dichloromethane, and neutralization with an aqueous $NaHCO_3$ solution, the organic phase is dried over Na_2SO_4, and the solvent is removed by vacuum distillation; the residue is then crystallized in ethanol. After storing the residue at -20°C, 15 mg (37%) of the product with a melting point of 141-144°C are isolated (Rf = 0.29 (dichloromethane:methanol = 90:10%).

The 12-(2-(N-BOC-L-alanyl)aminopropyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole used as precursor is synthesized as follows:

34 mg (0.1 mml [sic; mmol]) 12-(2-(3-aminopropyl))-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole are purified with stirring at room temperature with 25 mg (0.1 mmol) N-BOC-L-alanine-N-hydroxysuccinimidyl ester in 3 mL acetic acid and 1 mL DMF, and stirred for 3 h. The reaction solution is then diluted with 50 mL acetic acid and washed two times with water. After drying of the organic phase over Na_2SO_4 the solvent is removed by vacuum distillation and the raw product is used without additional purification for the next step. Rf = 0.62 (dichloromethane:methanol = 90:10%).

The 12-(2-(3-aminopropyl))-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole used as precursor is prepared as follows:

200 mg (0.5 mmol) 12-(2-cyanethyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole are hydrated in the presence of 250 mg Raney nickel (BK 111 W (Mo doped)) in 25 mL of a solvent mixture of methanol/sat. NH_3:THF = 1:2 with hydrogen at a pressure of 50-60 bar and a temperature of

60°C over a 48 h period. The reaction mixture is then filtered, the residue is washed three times with 10 mL methanol each time, the solvent is removed from the filtration in a vacuum, and the residue is precipitated from acetic acid. 100 mg (49%) of the products are isolated. Rf = 0.16 (dichloromethane:methanol = 90:10%).

The 12-(2-cyanethyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole used as precursor is prepared as follows:

a reaction mixture made of 4.6 g (11.7 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(cyanethyl)-1H-indol-3-yl)maleinimide, 4.4 g (23.3 mmol) p-toluenesulfonic acid hydrate and 3.8 g (16.7 mmol) DDQ in 600 mL toluene is heated for 2.5 h with reflux. The solvent is removed by vacuum distillation and the residue is separated by column chromatography (aluminum oxide/alkaline, acetone:ethanol = 95:5%). With the second fraction, 500 mg (11%) of the products are isolated in the form of a yellow powder. Rf = 0.69 (dichloromethane:methanol = 90:10%).

Example 9

12-(2-(L-alanyl-L-arginyl)aminopropyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole

The synthesis is conducted similarly to Example 4. However, the precursors used were 12-(2-(3-aminopropyl))-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-

c]carbazole and BOC-L-arginyl(Z2)-BOC-L-alanine. Melting point 164-166°C; Rf = 0.04 (chloroform:methanol:conc. NH_3 = 250:50:8).

Example 10

12-(2-(4-L-alanyl)aminobutyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole

The synthesis is conducted similarly to Example 9. Melting point 122-126°C; Rf = 0.17 (dichloromethane:methanol = 90:10%).

The 12-(2-(4-aminobutyl))-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo(2,3-a]pyrrolo[3,4-c]carbazole used as precursor is prepared as follows:

300 mg (0.7 mmol) 12-(2-(4-azidobutyl))-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole are hydrated in 40 mL of a solvent mixture consisting of THF:ethanol = 1:1 in the presence of 300 mg palladium on carbon (5%, anhydrous) at a pressure of 50 bar and a temperature of 25°C with hydrogen over a 24 h period. The reaction mixture is then filtered, the solvent is removed by vacuum distillation and the residue is stirred in ethanol. 250 mg (89%) of the product are isolated. Rf = 0.18 (chloroform:methanol:conc. NH_3 = 250:50:8).

The 12-(2-(4-azidobutyl))-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole used as precursor is prepared as follows:

a reaction mixture consisting of 1.6 g (3.7 mmol) 2-((1-methyl)-1H-indol-3-yl)-3-(1-(4-azidobutyl)-1H-indol-3-yl)

maleinimide, 1.4 g (7.4 mmol) p-toluenesulfonic acid hydrate and 1.25 g (5.5 mmol) DDQ in 500 mL toluene is heated for 30 minutes with reflux. The solvent is then removed by vacuum distillation, and the residue separated by column chromatography on (aluminum oxide/alkaline, acetone:ethanol = 95:5%). With the second fraction, 356 mg (22%) of the product are isolated as a light yellow powder. Rf = 0.88 (dichloromethane:methanol = 90:10%).

In a manner similar to Example 10 and the indicated method the following compound is prepared:

10a) 12-(2-(5-L-alanyl)aminopentyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole. Melting point 160-163°C; Rf = 0.27 (dichloromethane:methanol = 90:10%).

The compounds according to the invention are listed in Table III.

Table III

Beisp.	A	R^1	X	Y	E_n-R^5
1	Bisindol	CH_3	$(CH_2)_3$	NH	Ser
1a	Bisindol	CH_3	$(CH_2)_3$	NH	Ala
1b	Bisindol	CH_3	$(CH_2)_3$	NH	bAla
2	Bisindol	CH_3	$(CH_2)_3$	NH	DAla
2a	Bisindol	CH_3	$(CH_2)_4$	NH	Ala
2b	Bisindol	CH_3	$(CH_2)_4$	NH	Arg
2c	Bisindol	CH_3	$(CH_2)_5$	NH	Ala
2d	Bisindol	CH_3	$(CH_2)_9$	NH	Ala
2e	Bisindol	CH_3	$(CH_2)_9$	NH	Ser
2f	Bisindol	CH_3	$(CH_2)_8$	NH	Ala
2g	Bisindol	CH_3	$(CH_2)_8$	NH	Ser
3	Bisindol	CH_3	$(CH_2)_3$	NH	4Ava-Ser
4	Bisindol	CH_3	$(CH_2)_3$	NH	Gly-Ala
4a	Bisindol	CH_3	$(CH_2)_3$	NH	bAla-Ala
5	Bisindol	CH_3	$(CH_2)_2$	CO	Ala-OH
6	Bisindol	CH_3	$(CH_2)_2$	CO	Ala-O-CH_3
7	Bisindol	CH_3	$(CH_2)_2$	CO	Ala-Gly-Lys-NH_2
7a	Bisindol	CH_3	$(CH_2)_2$	CO	Lys-Asp-Arg-Phe-Ala-NH_2
7b	Bisindol	CH_3	$(CH_2)_2$	CO	Gly-Gly-Ala-NH_2
7c	Bisindol	CH_3	$(CH_2)_2$	CO	Gly-Gly-Ser-NH_2
7d	Bisindol	CH_3	$(CH_2)_2$	CO	Ser-Gly-Ala-NH_2
7e	Bisindol	CH_3	$(CH_2)_2$	CO	Gly-Gly-Gly-Ala-NH_2
7f	Bisindol	CH_3	$(CH_2)_2$	CO	Lys-Gly-Ala-NH_2
8	Carbazol	CH_3	$(CH_2)_3$	NH	Ala
9	Carbazol	CH_3	$(CH_2)_3$	NH	Ala-Arg
10	Carbazol	CH_3	$(CH_2)_4$	NH	Ala
10a	Carbazol	CH_3	$(CH_2)_5$	NH	Ala

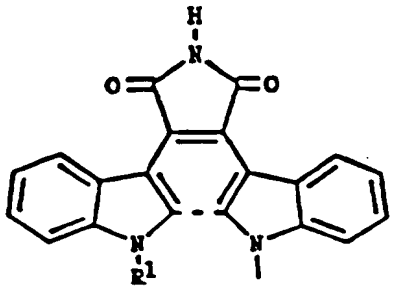
Key: 1 Example
2 Bisindole
3 Carbazole

Claims

1. Amino acid derivatives of the general formula I,

$$A\text{-}X\text{-}Y\text{-}E_n\text{-}R^5$$

in which A is a residue of the general formula III



where R^1 represents hydrogen or a lower alkyl residue with 1 to 4 carbon atoms and (- - -) can be open or can represent a bond;

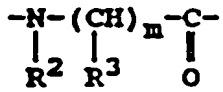
X represents a single bond or an alkylene group with 1-16 carbon atoms;

Y represents a single bond, a group such as N-R^2, CO, CS, CH=CH, PO(OH)O, SO_2, where

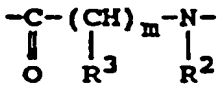
R^2 represents hydrogen or a lower alkyl residue with 1-4 carbon atoms, and

n = 1-20;

E represents either the same or different residues of the general formula IV



or of the general formula V



in which

R^2 represents a hydrogen or a lower alkyl residue with 1-4 hydrocarbons, and when

m = 1, the residue R^3 represents either hydrogen or the side group of one of the natural α-aminocarboxylic acids, and when m = 2-6, R^3 represents hydrogen; and

when E is a residue of the formula IV, R^5 represents an amino group or a residue $-OR^4$, in which R^4 represents a lower alkyl residue with 1-4 carbon atoms or hydrogen; and when E is a residue of the formula V, it represents hydrogen; as well as their pharmacologically acceptable salts.

2. Amino acid derivatives of the general formula I according to Claim 1, in which
A represents bisindolylmaleinimide or indolopyrrolocarbazole of the general formula III,
R^1 represents methyl,
X represents methylene, propylene, butylene, pentylene, octylene and nonylene,
Y represents either NH or CO, and the group $-E_n-R^5$ represents alanine, alanine methyl ester, ß-alanine, arginine, serine, glycylalanine, glycylglycylalanine, glycylglycylglycylalanine, glycylglycylserine, lysylglycylalanine, serylglycylalanine, alanylglycyllysine, lysylasparaginylarginylphenylalanylalanine, ß-alanylalanine, 4-aminovalerianoylserine or alanylarginine, as well as pharmacologically acceptable salts of acidic compounds of formula I with bases and salts of basic compounds of the general formula I with acids.

3. Compounds of the general formula I according to Claim 1, that is:
2-((1-methyl)-1-H-indol-3-yl)-3-(1-(3-L-serylaminopropyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-L-alanylaminopropyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-ß-alanylaminopropyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-D-alanylaminopropyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(4-L-alanylaminobutyryl)-1H-indol-3-yl)maleinimide;

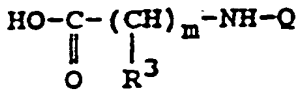
2-((1-methyl)-1H-indol-3-yl)-3-(1-(4-L-arginylaminobutyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(5-L-alanylaminopentyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(9-L-alanylaminononyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(9-L-serylaminononyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(9-L-alanylaminooctyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(9-L-serylaminooctyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(5-L-serylaminopentanoyl)-aminopropyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(L-alanylglycyl)aminopropyl)-1H-indol-3-yl)maleinimide;
2-((1-methyl)-1H-indol-3-yl)-3-(1-(3-(L-alanyl-ß-alanyl)aminopropyl)-1H-indol-3-yl)maleinimide;
3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-alanine;
3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-alanine methyl ester;
3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-alanylglycyl-L-lysinamide;
3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-lysyl-L-asparaginyl-L-arginyl-L-phenylalanyl-L-alaninamide;
3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionylglycylglycyl-L-alaninamide;

3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionylglycylglycyl-L-serylamide;
3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-serylglycyl-L-alaninamide;
3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionylglycylglycylglycyl-L-alanylamide;
3-(3-(4-(1-methylindol-3-yl)-1H-pyrrol-2,5-dion-3-yl)-indol-1-yl)propionyl-L-lysylglycyl-L-alanylamide;
12-[2-(3-L-alanyl)aminopropyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole;
12-(2-(L-alanyl-L-arginyl)aminopropyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole;
12-(2-(4-L-alanyl)aminobutyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole; and
12-(2-(5-L-alanyl)aminopentyl)-6,7,12,13-tetrahydro-13-methyl-5,7-dioxo-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole.

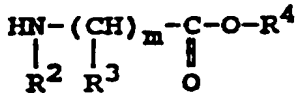
4. Method for the preparation of compounds I according to Claims 1-3, characterized by the fact that
a) for compounds in which n = 1, either compounds of the general formula VI

A-X-Y-G

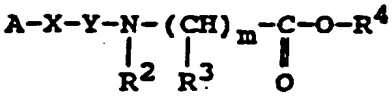
in which A and X have the meanings indicated above and -Y-G is an amino group are reacted with aminocarboxylic acids of the general formula VII



in which R^3 has the meaning indicated above and in which any functional groups present are provided with protecting groups and Q is an amino protecting group, followed by cleavage of the protecting group according to generally known methods, or
b) compounds of the general formula VI, in which A and X have the meaning indicated above and Y represents CO, CS, CH=CH, PO(OH)O or SO_2 and G is a hydroxy group or a halogen atom, are reacted with aminocarboxylic acids of the general formula VIII



in which R^2 and R^3 have the meanings indicated above and R^4 is a methyl, ethyl or propyl group, to compounds of the general formula IX

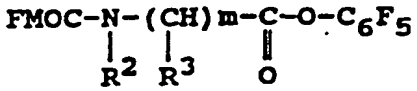


in which R^2, R^3 and R^4 have the meanings indicated above, or

c) when the compounds of the general formula VI are in the form of carboxylic acids, for the purpose of the reaction with compounds of the general formula VIII, the carboxylic acids are converted under the usual conditions to activated esters and then the compounds of the general formula IX are converted by alkaline saponification of the ester group to compounds of the general formula I,

or

d) for compounds of the general formula I, in which A, X and Y have the meanings indicated above and E_n for $n > 1$ represents a peptide group, characterized in that either compounds of the general formula I are reacted according to the generally known methods with additional aminocarboxylic acids, or by conducting the synthesis of compounds of the general formula I on solid phases according to the Merrifield method, where the first amino acid of the general formula XI



in which R^2 and R^3 have the meanings indicated above, is added to the Merrifield resin by condensation, and then the fluorophenylmethyloxycarbonyl protecting group is cleaved according to generally known methods and subsequently, depending on the need, additional aminocarboxylic acids of the general formula XI are added by condensation, and in the last

condensation step, compounds of the general formula VI in which A and X have the above-indicated meanings, Y represents CO or CS and G represents a hydroxy group, in the presence of carboxylic acid activated compounds, are reacted with the peptide attached to the Merrifield resin; or

e) when compounds having the general formula VI, in which A and X have the meanings indicated above and Y represents N-R^2 and G is hydrogen, these compounds are reacted with aminocarboxylic acids of the general formula VII, by placing an aminocarboxylic acid of the general formula VII into an aprotic solvent and converting it with pentafluorophenol or N-hydroxysuccinimide, preferably with dicyclohexylcarbodiimide and in the presence of hydroxybenzotriazole, to an active carboxylic acid ester, and then, in the same solvent, the compounds of the general formula VI are reacted at temperatures between 0-60°C; or

f) compounds of the general formula I, in which A and X have the meanings indicated above and E represents a terminal carboxylic acid group, are prepared by converting compounds of the general formula VI, in which A and X have the meanings indicated above, Y represents CO or CS and G represents a hydroxy group, in an appropriate solvent with pentafluorophenol or N-hydroxysuccinimide, preferably with dicyclohexylcarbodiimide and in the presence of hydroxybenzotriazole, to an active carboxylic acid ester, followed by a reaction in the same solvent with compounds of the general formula VIII at temperatures between 0-60°C; or

g) for compounds of the general formula I, in which A and X have the above-indicated meaning, Y is a carbonyl group and E_n for n >

1 represents a peptide group, aminocarboxylic acids of the general formula XI, in which R^2 and R^3 have the meanings indicated above, are added by condensation, in aprotic solvents and in the presence of hydroxybenzotriazole, to Merrifield resins, followed by the washing out of reagents with the appropriate solvent, cleavage of the fluorenylmethyloxycarbonyl protecting group under alkaline conditions, again washing out of residual reagents, and the addition by condensation in this manner of additional aminocarboxylic acid and, as a last partial compound, a compound of the general formula VI, in which A and X have the meanings indicated above, Y represents CO, and G represents a hydroxy group, is the compound added by condensation in the same manner, and the compound is isolated by treatment of the Merrifield resin with a strong acid for several hours at room temperature, followed by separation of the resulting solution and isolation, after removal of the solvent, of the products in solid form from ether.

5. Drug containing compounds of the general formula I according to Claims 1-3, in addition to the usual adjuvants and additives.

6. Use of compounds of the general formula I according to Claims 1-3 for the preparation of drugs for the treatment and/or prevention of cancer, viral diseases, cardiac and vascular diseases, thromboses, cardiac rhythm disorders, atherosclerosis, bronchopulmonary diseases, degenerative diseases of the central nervous system, inflammatory diseases, diseases of the immune system, psoriasis or for use as an immunosuppressant.

7. Use of compounds of the general formula I according to Claims 1-3 for the treatment and/or prevention of cancer, viral diseases, cardiac and vascular diseases, thrombosis, cardiac rhythm disorders, atherosclerosis, bronchopulmonary diseases, degenerative diseases of the central nervous system, inflammatory diseases, diseases of the immune system, and psoriasis or use as an immunosuppressant.